Full title of trial	Does pre-operative D-chart score predict improvement in VFQ-25 score following surgery for epiretinal membrane?
Short title	'Distortion as a predictor of ERM surgery outcome'
Version and date of protocol	Version 7.8 01.10.2019
Sponsor:	NHS GGC
Sponsor protocol number	GN18OP439
IRAS Project ID	246530
Funder (s) :	Royal College of Surgeons of Edinburgh (Ophthalmology Small Research Grant awarded March 2019)
Sites(s)	Gartnavel General Hospital Glasgow G12 0YN UK Note: Idea is to collaborate with hospitals in England and Madrid in the future, after Glasgow study has been set up

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Signatures

The Chief Investigator and the R&D have discussed this protocol. The investigators agree to perform the investigations and to abide by this protocol.

Chief investigator

Dr Yorston
TIO

Signature Date

Sponsor Representative

Signature Date

This Protocol template is intended for use with Glasgow site only (other UK sites, and Spanish site, might be recruited at later stage)

Contents

List of abbreviations

AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
GCP	Good Clinical Practice
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSC	Trial Steering Committee

1 Trial personnel

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2 Summary

Research question	Does pre-operative D-chart score predict improvement in VFQ-25 score following surgery for epiretinal membrane?
Title:	Predictive value of pre-operative distortion score for improvement in vision-related quality of life following epiretinal membrane surgery
Short title:	Change in VFQ-25 following ERM surgery
Trial medication:	No medications. Trial of surgery.
Objectives:	Primary: To assess how pre-op D chart score correlates with VFQ-25 scores 26 and 52 weeks after surgery. Secondary: To summarise the changes over time (i.e. from pre op, to 26 then 52 weeks after the surgery) of the following variables: i. D-chart score ii. BCVA (ETDRS) iii. VFQ-25 iv. Central retinal thickness obtained from OCT scans
Type of trial:	Prospective case series consisting of patients with symptomatic epiretinal membranes presenting to vitreoretinal department in a tertiary referral centre.
Trial design and methods:	The study group will include patients who choose to undergo surgery for epiretinal membrane peel +/- cataract surgery. The following data will be collected pre-operatively: demographics (age, gender), laterality, duration of symptoms, lens status (clear lens/ cataract/ PCIOL), past ophthalmic history, BCVA, central retinal thickness, degree of distortion, vision-related quality of life. The patients are typically seen at Day 1 and Week 1/2 after the surgery. They will be seen at 26 weeks and 52 weeks after surgery for the assessment of:

	i) their retinal function (visual acuity and assessment of distortion) and retinal imaging (OCT), and ii) their vision-related quality of life Symptoms of distortion will be quantified and characterised using a novel methodology used previously in patients with retinal detachments and macular holes (D Chart). NEI VFQ-25 quality of life questionnaire will be used to measure the vision-related quality of life.
Trial duration per participant:	12 months
Estimated total trial duration:	24-36 months
Planned trial sites:	Tennent Institute of Ophthalmology, Gartnavel Hospital, Glasgow UK
Total number of participants planned:	60-70 (2/3 of 80-100)
Main inclusion/exclusion criteria:	**Principal Inclusion Criteria**: • Idiopathic epiretinal membrane • Patients undergoing epiretinal membrane surgery, under local or general anaesthetic • Able to give informed consent • 18 years old and over **Principal Exclusion Criteria**: • Epiretinal membrane secondary to retinal detachment, uveitis or retinal vascular disease • Previous vitreoretinal surgery • Pre-existing ophthalmic condition other than epiretinal membrane which limits the patient's visual acuity (documented BCVA 6/36 or worse) • Pre-existing ophthalmic condition other than epiretinal membrane which cause metamorphopsia (e.g. exudative ARMD, central serous retinopathy) • VA < 6/60

Statistical methodology and analysis:	The study statistician will be responsible for statistical aspects of the trial from design through to analysis and dissemination. Regression analysis will be used to determine the relationship between D chart scores and VQF-25 scores 26 and 52 weeks post-surgery while correcting for baseline VFQ-25 scores. Changes over time in D chart scores, BCVA (ETDRS), VFQ-25 and central retinal thickness will be summarised graphically with appropriate descriptive statistics. All statistical analyses will be done using Minitab (version 18) at a 5% significance level.

3 Introduction

3.1 Background and literature review

Epiretinal membranes result from an anomaly of the vitreoretinal interface. They consist of a proliferation of avascular fibrocellular tissue along the inner limiting membrane of the retina, and are thought to arise from retinal glial cells that have been liberated during a precipitating event such as a posterior vitreous detachment or surgery. Risk factors for ERM include ageing, intraocular surgery/ cryotherapy, inflammation, vascular ischaemic disease trauma and retinal detachment – idiopathic cases make up a significant proportion of the patient population. About 6% of those over the age of 50 years have an epiretinal membrane [1]. Over time, this membrane can result in anterior-posterior traction, intraretinal cystic changes and macular detachment [2]. The patient may become symptomatic with distorted vision, with straight lines appearing bent or wavy, or blurred vision.

Management of epiretinal membrane includes observation (over 75% of patients stabilise after diagnosis) or surgery for severely symptomatic membranes. The surgery consists of vitrectomy and epiretinal +/- inner limiting membrane peel.

Literature review

60-85% of patients undergoing epiretinal membrane surgery experience a significant improvement in quality of life. Patients with ERM now constitute one of the most common referrals to the vitreoretinal service. Being able to identify the patients who are the most likely to experience an improvement from ERM surgery, and to quantify this improvement, would be of practical help to both the patient and the surgeon. For the patient, this would help weigh up the benefits and risks of proceeding with an elective operation.

Numerous studies have shown that epiretinal membrane surgery leads to an improvement in visual acuity [3,4,5]. Dawson et al [3] showed that patients with better initial VA achieved better final VA outcome, but that patients with poorer pre-op VA showed greater change in VA following surgery. Some studies have advocated patient selection based on pre-operative visual acuity. A retrospective study of 40 cases by Thompson [6] concluded that surgery for ERM is beneficial in pseudophakic eyes with relatively good preoperative visual acuities (better than 20/60). Rahman et al [7] compared patients with 'early' ERM (pre-operative logMAR score < 0.3) and 'medium' or 'late' ERM (logMAR score of 0.4 & 0.5, and score of > 0.6 respectively), and showed that the 'early' ERM group had better mean postoperative logMAR score, and a greater proportion achieved of that group achieved a logMAR visual score of < 0.1.

However, it has also been shown that vision-related quality of life can improve even in the absence of improvement in visual acuity [8]. This implies that surgery improves aspects of visual function other than acuity, such as metamorphopsia and aniseikonia [8]. Therefore some patients who are experiencing these symptoms might still be good candidates for surgery in spite of having relatively good visual acuity.

Numerous tests exist to measure the degree of metamorphopsia such as the M-chart and the Foresee monitoring programme. Recently, the D-chart, which aims to overcome some of the limitations of the other existing tests, was developed in Glasgow in collaboration with Glasgow Caledonian University by some of the authors of this study

[1]. This test has been shown to be consistent and practical (taking patients 5-10 minutes to complete).

A few studies have been published on metamorphopsia and quality of life in patients undergoing ERM surgery. Ghazi-Nouri et al [8] prospectively followed 20 patients undergoing epiretinal membrane surgery, looking at the effect on visual acuity, contrast sensitivity, metamorphopsia (using an Amsler chart) and health-related quality of life (using the VFQ-25 and SF36 questionnaires). Ichikawa et al [9], Kinoshita et al [10], and Okamoto et al [11] studied pre- and post-op metamorphopsia using M-charts. However, these studies are limited by small numbers (<30 eyes) and short follow-up (< 4 months) [8,9,11] and retrospective nature [9]. Validated vision-related quality of life questionnaires were not always used [9,10] and none of the studies measured metamorphopsia using the D-chart, which we believe to be a superior tool.

As our study measures the effects on distortion (using D chart), visual acuity and quality of life from ERM surgery, it will allow us to investigate whether the pre-op D chart score can predict subsequent improvement in quality of life following surgery. This will provide vitreoretinal surgeons and patients with an evidence base regarding the success of this elective procedure and offer realistic expectations regarding surgical outcomes. Ultimately, we hope that the results of this study will facilitate the decision of whether or not to proceed with ERM surgery.

3.2 Clinical data

a. Measurement of Distortion

The D Chart system [12] will be used to measure distortion. This method consists of 24 test plates each of which assess four concentric zones around the point of fixation (0.0-1.5, 1.5-3.5, 3.5-7.0, and 7.0-12.0 degrees from fixation). The severity of distortion, in degrees is assessed in each zone at a number of fixed points. A 'D-score' is then calculated which reflects both the number of locations within that zone where distortion is perceived, and the severity of that distortion. This approach has been used in patients with distortion secondary to other retinal pathologies (epiretinal membranes, macular holes and retinal detachments) [12] and been found to be consistent and practical (taking patients 5-10 minutes to complete).

b. Measurement of vision-related quality of life

The National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25) will be used as a measure of patient-reported, vision-related functioning. This questionnaire is the product of the longer field test version of the survey called the 51-item National Eye Institute Vision Function Questionnaire [13], and was developed to measure the range of vision-related functioning experienced by persons with a variety of chronic eye diseases. It has been used in a number of studies to measure the health-related quality of life related to vision in patients with diabetes [14], dry eyes [15], age-related macular degeneration [16] and visual impairment in the elderly [17], as well as for patients undergoing ERM surgery [8].

3.3 Rationale and risks/benefits

Research Question:

Does pre-operative D-chart score predict improvement in VFQ-25 score following surgery for epiretinal membrane?

Exploratory aims are to:

- To investigate the sustained effect of epiretinal membrane surgery on distortion and BCVA
- To determine the relationship between distortion and vision-related quality of life

The decision regarding whether to proceed with surgery will be made by the patient. Participation in the study will mean one additional visit .Appointment times will also be slightly longer in order to allow measurement of distortion (estimated to take around 5 minutes per eye) and vision-related quality of life. However this study is an observational one and designed to record the patient experience rather than influencing it.

3.4 Assessment and management of risk

This study does not expose the patients to a higher risk than standard medical care.

Once the patient has decided to participate in the study, they will receive the same standard of care as any other patient who decides to pursue epiretinal membrane surgery, with some additional observational tests (use of D-chart for measurement of

distortion and administration of VFQ-25 questionnaire), and therefore are not exposed to any other additional risk.

4 Objectives

Primary:

To assess how pre-op D score correlates with VFQ-scores 26 weeks and 52 weeks after epiretinal membrane surgery.

Secondary:

To summarise the changes over time (i.e. from pre op, to 26 then 52 weeks after the surgery) of the following variables:

v. D-chart score
vi. BCVA (ETDRS)
vii. VFQ-25
viii. Central retinal thickness obtained from OCT scans

5 Trial design

5.1 Overall design

This non-commercial prospective interventional case series aims to determine whether it is possible to predict the amount of improvement in vision-related quality of life that a patient will experience following ERM surgery, from a pre-operative measurement of distortion.

Around 60-70 patients will be recruited in Glasgow. The decision regarding whether to proceed with surgery will be made by the patient, and following enrolment onto the study they will receive standard care.

Standard 3 port pars plana vitrectomy and epiretinal membrane and ILM peel with gas tamponade will be performed. Phakic patients will undergo cataract surgery. Any intraoperative or postoperative complications will be recorded.

Any patient undergoing epiretinal membrane surgery is routinely reviewed at Day 1 and Week 1/2. The study visits are at 26 weeks (+/- 8 weeks) and 52 weeks (+/- 8 weeks). A full clinical examination will be performed at each visit. At the 26 and 52-week follow

ups, bilateral OCT and D-chart assessments will be performed. VFQ-25 will also be assessed at 26 and 52-week follow ups.

Visual improvement following epiretinal membrane surgery is thought to continue for up to 1-2 years after surgery. At our centres patients having undergone epiretinal membrane surgery tend to be discharged around the 6-month post-operative period, with advice to the patient regarding likelihood of gradual continued improvement in distortion. In this trial, involvement of individual participants will be for a maximum of 12 months.

5.2 Unit of Analysis

There will be one eye recruited per study patient. The operated eye will be the study eye, and the eye related outcome measures will be for that eye only. If the patient presents with bilateral epiretinal membranes, then, provided both eyes satisfy the inclusion criteria, one eye will be randomly selected for the study.

6 Selection of Subjects

6.1 Inclusion criteria

a) Idiopathic epiretinal membrane
b) Patients undergoing vitrectomy and gas surgery, under local or general anaesthetic
c) Able to give informed consent
d) 18 years old and over

6.2 Exclusion criteria

a) Epiretinal membrane secondary to retinal detachment, uveitis or retinal vascular disease
b) Previous vitreoretinal surgery
c) Pre-existing ophthalmic condition which limits the patient's visual acuity (Documented BCVA 6/36 or worse)
d) Pre-existing ophthalmic conditions which cause metamorphopsia (exudative ARMD, central serous retinopathy)
e) VA < 6/60

7 Recruitment

Patients will be recruited from the vitreoretinal clinics at the Tennent Institute of Ophthalmology in Glasgow, UK.

The doctors working in these clinics will be informed in advance about the trial. Posters will be placed in the clinic rooms to serve as a reminder. There will be no advertising directly to patients or outside the clinic setting.

8 Study procedures and schedule of assessments

8.1 Informed consent procedure

Consent for the trial will be taken by the principal or co-investigator or person delegated by the investigator (study doctor or research nurse). These persons will have been GCP trained, will be fully informed regarding the trial and be trained in taking informed consent. Persons eligible to take consent will be specified in the delegation log. Written consent will be obtained from each subject prior to participation in the trial, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study.

Patients will undergo a routine assessment with the clinical care team. During this assessment if it becomes apparent that the patient is eligible for the study, the clinical care team will inform the research team. Some of the data from this assessment (which will be obtained prior to informed consent being taken) will be used to complete baseline demographics on the CRF by the study team.

Patients identified as being eligible for the study in the vitreoretinal clinic will have the opportunity to discuss the trial in advance of their surgery. Should they be confirmed as being eligible and wish to proceed, a consent form will be signed in advance of their surgery and the patient will be given a copy of the consent form.

At the completion of the epiretinal membrane surgery, the operating surgeon will confirm that the patient remains eligible for the trial.

No clinical trial procedures will be conducted prior to taking consent from the participant. Consent will not denote enrolment into trial.

If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary. All subjects, including those already being treated, will be informed of the new information, giving a copy of the revised form and give their consent to continue in the study.

If a participant who has given informed consent loses capacity to consent during the study, they would be withdrawn from the study. Identifiable data or tissue already collected with

consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.

Interval between patients being informed about trial and commencement. Patients with possible epiretinal membranes will attend a routine vitreoretinal clinic (screening visit). This visit will include only assessments that are part of the standard clinical care of patients prior to epiretinal membrane surgery, namely:

- History of ocular disease
- Previous vitreoretinal surgery
- Clinical examination: evidence of epiretinal membrane

Patients with an epiretinal membrane who choose to proceed with surgery will be scheduled for non-urgent surgery (usual waiting time 2 weeks to 3 months). Consent for participation in the study will be taken at this initial clinic visit. There will therefore be adequate time for the patient to consider their involvement and study the patient information sheet prior to the operation.

Withdrawal. The investigator, or designee, will explain to patients that they are under no obligation to enter the trial and can withdraw at any time without having to provide an explanation.

Documentation of consent. A copy of the signed consent form will be given to the participant. The original form will be retained at the study site and a copy placed in the medical notes.

New developments. If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary. All subjects, including those already being treated, will be informed of the new information, giving a copy of the revised form and give their consent to continue in the study.

8.2 Baseline visit

After having been listed for surgery at the initial clinic visit (screening visit), the patient will be seen at the pre-operative assessment clinic (baseline visit). At this visit, the research nurse will obtain informed consent and carry out the protocol assessments as per table 8.3.

Surgery will occur within 28 days of the baseline visit.

8.3 Assessment timeline

		Screening	Baseline	Follow-up		
Visit #		**1**	**2**	**3**	**4**	**5**
		Initial Clinic	Pre-op assessment	Week 2 post-op	Week 26 post op (+/- 8 weeks)	Week 52 post op (+/- 8weeks)
Seen by doctor		*X*		X	X	X
Eligibility determination		*X*				
Seen by Research Nurse			*X*		X	X
Informed Consent			*X*			
Protocol Assessments	**BCVA (ETDRS)**		X	*X*	X	X
	OCT		X		X	X
	D-chart		X		X	X
	VFQ-25		X		X	X
Adverse Events review				*X*	X	X

Baseline assessments

BCVA (ETDRS) and slit lamp/indirect ophthalmic examination (anterior segment assessment, lens status, presence and severity of epiretinal membrane).

Subsequent assessments

Adverse events:

To be documented in patient casenotes at the 2 and 26-week follow up appointments, and transcribed to Case Report Form Appendix 5 (Adverse Event Reporting Form) by research nurses.

Follow-up visits:

- Best-corrected ETDRS visual Acuity. This assessment is part of standard clinical care and non-invasive.
- Macular OCT imaging. This assessment is part of standard clinical care and non-invasive.
- Assessment of distortion (D-Chart). This non-invasive test requires patients to view a series of charts and describe distortion where seen.
- Visual function questionnaire

8.4 Definition of end of trial

The trial will end on the date of the last 52-week follow up visit by the last participant.

8.5 Discontinuation/withdrawal of participants and 'stopping rules'

Circumstances for patient withdrawal from trial:

- Patient choice - If at any time the patient decides to withdraw from the study after giving informed consent they may do so at any time and without giving reason. The patient will be advised that their standard of care will not be affected should they withdraw from the study.
- Development of other conditions that could cause metamorphopsia or loss of vision e.g. AMD

Documentation in event of withdrawal:

- Reason for withdrawal

If patients are withdrawn or discontinue the trial, they will be asked if they are willing to attend the 26-week visit, in which they will undergo the planned 26-week assessments.

It is not intended that withdrawn subjects be replaced, but their permission will be asked for their data to be used as part of an intention to treat analysis. The trial would be stopped prematurely in the event of new information that undermined the validity of the research.

9 Treatment of subjects

This study will involve following up patients who have chosen to undergo epiretinal membrane surgery. The patients will receive standard surgical treatment. Furthermore, it does not evaluate any medicinal product, medical device, food supplement, radiation, surgery or behavioural interventions.

Post-operative medications - routine topical antibiotic, steroids and mydriatics which are part of the standard post-operative care.

10 Recording and reporting of adverse events and reactions

10.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject undergoing the study intervention and which does not necessarily have a causal relationship with this intervention.

Adverse Reaction (AR)	Any untoward and unintended response in a subject to the study intervention which **is related** to any study intervention.

Term	Definition
Serious adverse event (SAE), serious adverse reaction (SAR) or unexpected serious adverse reaction	Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that: • results in death, • is life-threatening, • requires hospitalisation or prolongation of existing hospitalisation,

	• results in persistent or significant disability or incapacity, or • consists of a congenital anomaly or birth defect
Important Medical Event	These events may jeopardize the subject or may require an intervention to prevent one of the above characteristics/consequences. Such events should also be considered 'serious'.
Unexpected adverse reaction	An adverse reaction the nature and severity of which is not consistent with the study intervention.
SUSAR	Suspected Unexpected Serious Adverse Reaction

10.2 Recording adverse events

Adverse events will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate. Adverse events noted up to and during the last study visit will be recorded.

Adverse events will be recorded for study patients up until their final study visit at 12 months.

Regarding Ocular Adverse Events

All ocular adverse events (AEs) reported by patients and observed by the study team will be recorded in the medical records and CRF following randomisation until the patient has completed their final study visit at 12 months. The exception to this will be events which are inevitable consequences of the surgical intervention (refer to later in text for examples). These events will only be recorded in the medical records.

Expected Ocular AEs to be recorded in the CRF& Medical Notes:

1. Elevated intraocular pressure (IOP)(see below)
2. Hypotony (IOP <6mmHg)
3. Retinal detachment
4. Further ocular surgery
5. Endophthalmitis
6. Uveitis occurring more than 4 weeks after surgery

More specifically, the following definition of elevated IOP will be used for this study:

Mild: >25mmHg – 35mmHg

Moderate: >35mmHg

Severe: Any interventional invasive procedure (eg. surgery or laser) required to control IOP acutely or long-term, during the study period.

Expected Ocular AEs to be Recorded in Medical Notes Only:

These will not be considered adverse events, as they are expected findings in this disease population and as such will only be recorded in the medical notes. Reporting these findings as AEs are not deemed to add additional safety data to the study.No electronic record of these events will be kept. Examples include:

Subconjunctival haemorrhage, conjunctival chemosis, periorbital oedema, routine postoperative pain, cataract formation, corneal epithelial defect secondary to intraoperative epithelial debridement, CMO. If any of the above events occur to a severity or duration that is unexpected by the PI, they may then be reported as AE's, making clear the reason (e.g. 'prolonged post-operative pain' or 'severe subconjunctival haemorrhage').

Regarding Non-Ocular Adverse Events

Expected Non-Ocular AEs, Recorded in CRF & Medical Notes:

None expected

10.3 Assessments of Adverse Events

Each adverse event will be assessed for the following criteria:

10.3.1 Severity

Category	Definition
Mild	The adverse event does not interfere with the volunteer's daily routine, and does not require intervention; it causes slight discomfort
Moderate	The adverse event interferes with some aspects of the volunteer's routine, or requires intervention, but is not damaging to health; it causes moderate discomfort
Severe	The adverse event results in alteration, discomfort or disability which is clearly damaging to health

10.3.2 Causality

The assessment of relationship of adverse events to the study protocols is a clinical decision based on all available information at the time of the completion of the case report form. The following categories will be used to define the causality of the adverse event:

Category	Definition
Definitely:	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Probably:	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Possibly	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of

	the trial related procedures). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant events).
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial related procedures). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatments).
Not related	There is no evidence of any causal relationship.
Not Assessable	Unable to assess on information available.

10.3.3 Expectedness

Category	Definition
Expected	An adverse event that is classed in nature as serious and which is clearly defined in this protocol.
Unexpected	An adverse event that is classed in nature as serious and which has not been anticipated and specified in this protocol.

The protocol will be used as the reference document to assess disease related and/or procedural expected events.

10.3.4 Seriousness

Seriousness as defined for an SAE in section 10.1.

10.4 Procedures for recording and reporting Serious Adverse Events

Reportable SAEs:

An SAE occurring to a research participant will be reported both to the sponsor via an SAE form at the following email address: pharmacovig@glasgowctu.org, and to the main REC within 24 hours of becoming aware where in the opinion of the Chief or Principal Investigator the event was:

• Related – that is, it resulted from administration of any of the research procedures, and

• Unexpected – that is, the type of event is not listed in the protocol as an expected occurrence. (Expected Adverse Events are listed in 10.2.)

***Recordable SAEs**:*

Ocular events that meet the definition of serious, but are expected (see section 10.2), will be recorded in the medical notes and the CRF as an SAE, but not immediately reported as an SAE to the sponsor. Examples include further ocular surgery (e.g. cataract surgery).

Non-ocular events that meet the definition of serious will be recorded in the hospital notes but only recorded in the CRF if they are thought to be possibly, probably or definitely related to epiretinal membrane surgery. They will only be immediately reported to the sponsor as an SAE if they are not expected (see section 10.2).

The events will be recorded in the study SAE log and submitted to the Sponsor on a monthly basis using the following email address: pharmacovig@glasgowctu.org and an SAE form will not be completed. However, if any of the above events require unexpected urgent surgery and the investigator deems the event to be possibly related to epiretinal membrane surgery, they will be considered a reportable SAE and will be immediately reported to the sponsor (within 24hours).

Examples of recordable& reporting AEs&SAEs:

Clarification for recording and reporting non-ocular AEs:

a) Coryzal illness not satisfying criteria for serious – record in medical notes only.
b) A fall resulting in a fractured wrist, requiring a hospital admission and urgent surgery to repair – record in medical notes only.
c) Further ocular surgery for retinal detachment during the study period – record in medical notes AND log in CRF. Record as an SAE, but do not immediately report to sponsor.

10.4.1 Notification of deaths

All deaths will be reported to the sponsor irrespective of whether the death is related to disease progression, trial procedures, or an unrelated event. This report will be immediate.

10.4.2 Reporting SUSARs

The sponsor will notify the main REC of all SUSARs within 15 days after the sponsor has learned of them.

10.4.3 Development Safety Update Reports

Not Applicable

10.4.4 Annual progress reports

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended.

The research coordinator will prepare the APR.

10.4.5 Reporting Urgent Safety Measures

If any urgent safety measures are taken the PI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice the relevant REC of the measures taken and the circumstances giving rise to those measures.

10.4.6 Notification of Serious Breaches to GCP and/or the protocol

A "serious breach" is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial.

The sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of:

(a) the conditions and principles of GCP in connection with that trial; or (b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach.

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase. The sponsor's SOP on the 'Notification of violations, urgent safety measures and serious breaches' will be followed.

11 Data management and quality assurance

11.1 Confidentiality

All data will be handled in accordance with the General Data Protection Regulation..

The Case Report Forms (CRFs) will not bear the subject's name or other personal identifiable data. Trial number will be used for identification on the CRFs. The chief investigator or delegated authorised individual will be responsible for keeping a separate log file which links the study ID and the patient's details and will be kept on a protected computer.

11.2 Data collection tools and source document identification

The investigator will work with the trial team to maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, results of OCT scans, D-chart assessments and visual function questionnaire.
A subset of the information in the source documents will be determined by the chief investigator and other suitably trained members of the study team to be the trial dataset for the Case Report Forms (CRFs). This will be agreed with the study statistician and communicated to the R&D IT team. CRFs will be designed and produced by the R&D IT Team according to the sponsor's CRF template. All data will be entered legibly in black ink with a ball-point pen. If an error is made, the error will be crossed through with a single line in such a way that the original entry can still be read. The correct entry will then be clearly inserted, and the alterations will be initialed and dated by the person making the alteration. Overwriting or use of correction fluid will not be permitted. The completion of CRFs will be signed off by the Chief Investigator or delegated authorized individual (Principal Investigator) as outlined in the delegation log. The delegation log will identify all those personnel with responsibilities for data collection and handling. It will be the responsibility of the investigator to ensure the accuracy of all data recorded on the CRFs.

All information on CRFs must be traceable to the source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

11.3 Data handling and analysis

The completed CRFs will be checked for completion by the research nurse / research manager. The delegated authorised individual will then enter data onto the trial database created by the R&D IT team. Data entry will be carried out within 1 week of CRF completion. When all patients have been recruited, the R & D data officer will double data enter 10 CRFs randomly selected by the senior data manager, plus 100% of primary outcome data for all patients. The first and second data entries will be compared for completion and consistency checks will be performed. The error rate will be calculated and errors will be corrected as necessary. Sense checks, logic checks and range checks will be performed. Data queries will be corrected and data will be cleaned. When all parties agreed and signed the data lock request – sign off form with reference to DM_S04 clinical trial data validation, data cleaning and database lock. The database will then be locked and data transferred for analysis by trial statisticians using STATA statistical software. Data management process will follow the trial data management plan.

Data handling will be performed adhering to the General Data Protection Regulation..

12 Record keeping and archiving

Archiving will be authorised by the Sponsor following submission of the end of study report.

Chief Investigators are responsible for the secure archiving of essential trial documents for each site and the trial database as per their trust policy. All essential documents will be archived for a minimum of 5 years after completion of trial.

Destruction of essential documents will require authorisation from the Sponsor.

13 Statistical Considerations

The study statistician who will be responsible for statistical aspects of the trial from design through to analysis and dissemination.

13.1 Outcomes

13.1.1 Primary outcome

VFQ-25 score at final visit (52 weeks after ERM surgery)

13.1.2 Secondary outcomes

Descriptive statistics and graphs as appropriate for the following variables, pre-operatively and at 26 and 52 weeks after ERM surgery:

i. D-chart score
ii. BCVA (ETDRS)
iii. VFQ-25 score
iv. Central retinal thickness obtained from OCT scans

13.1.3 Exploratory outcomes

Correlation between pre-operative D-chart score and VFQ-25 score 26 and 52 weeks after ERM surgery

13.2 Sample size and recruitment

13.2.1 Sample size calculation

All available patients over a 12-month period will be targeted. About 80 to 100 patients have ERM surgery in a year in Gartnavel General Hospital. We would except to enrol about two thirds of these (i.e. about 60 patients in total). This should allow us to detect a correlation of about 0.345 with 89% power.

13.2.2 Planned recruitment rate

A total of 60-70 patients will be entered into the study in Gartnavel General Hospital. To recruit these patients over 12 months, we would need to recruit 5-6 patients per month, which based on the audit data, should be achievable across both sites.

13.3 Statistical analysis plan

Regression analysis will be used to determine the relationship between D chart scores and VQF-25 scores at 26 and 52 weeks post-surgery while correcting for baseline VFQ-25 scores. Changes over time in D chart scores, BCVA (ETDRS), VFQ-25 and central retinal thickness will be summarised graphically with appropriate descriptive statistics. All statistical analyses will be done using Minitab (version 18) at a 5% significance level.

13.3.1 Summary of baseline data and flow of patients

Summary statistics will be presented as mean and standard deviation for continuous (approximate) normally distributed variables, median and interquartile range for non-normally distributed variables and frequency and percentage for categorical variables.

13.3.2 Primary outcome analysis

The primary outcome is the VFQ-25 score 52 weeks after the ERM surgery.

13.3.3 Secondary outcome analysis

Summary statistics for all secondary outcomes will be presented. Where appropriate the standard error and two-sided 95 % confidence interval will be presented. For outcome measures which are presented as proportions, a 95 % confidence interval will be computed by the exact binomial method.

13.3.4 Exploratory outcome analysis

Regression analysis will be used to determine the relationship between pre-op D chart scores and VQF-25 scores 26 and 52 weeks post-surgery while correcting for baseline VFQ-25 scores.

It is inevitable that some patients will be lost to follow-up, for example due to changes in health, social or personal circumstances. In cases of missed appointments, the research nurse will contact the participant by phone, and then by post. The reason for missing the appointment will be documented, and, where possible, a more convenient follow up will be arranged. The chief investigator will be informed by email of any patients lost to follow up. If data are missing for any patients, reasons for this may be important and these will be investigated using logistic regression of covariates on an indicator of missingness. If there are less than 5 % missing data and data appear to be missing completely at random, we may report the available case analysis as our main analysis. Sensitivity analysis will however be conducted allowing a best and worst case scenarios and these results reported alongside the available case report.

Please note that a more detailed statistical analysis plan should be produced as a separate document at some point prior to the final analysis (as recommended by the ICH E9 guidelines). In this document, a more technical and detailed elaboration of the principal features stated in the protocol should be included. The plan may include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data. The plan should be reviewed and possibly updated as a result of the masked review of the data and should be finalized before breaking the mask. Formal records should be kept of when the statistical analysis plan was finalized as well as when the mask was subsequently broken.

13.4 Interim analysis

No interim statistical analyses are planned.

13.5 Other statistical considerations

Any deviations from the statistical analysis plan will be described and justified in the final report, as appropriate.

14 Name of Committees involved in trial

Trial Steering Committee (TSC): consisting of principle and co-investigators, research coordinator and statistician.

15 Direct Access to Source Data/Documents

The investigator(s)/ institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Study participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

16 Ethics and regulatory requirements

The sponsor will ensure that the study protocol, patient information sheet, consent form, and submitted supporting documents have been approved by a main research ethics committee, prior to any patient recruitment. The protocol and all agreed substantial protocol amendments will be documented and submitted for ethical approval prior to implementation.

Before the site can enrol patients into the trial, the Chief Investigator/Principal Investigator or designee must apply for NHS permission from their Trust Research & Development (R&D) and be granted written permission. It is the responsibility of the Chief Investigator/ Principal Investigator or designee at each site to ensure that all subsequent amendments gain the necessary approval. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual patients (see section 10.4.5 for reporting urgent safety measures).

Within 90 days after the end of the trial, the CI/Sponsor will ensure that the main REC are notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The CI will supply the Sponsor with a summary report of the clinical trial, which will then be submitted to the main REC within 1 year after the end of the trial.

17 Monitoring requirement for the trial

18 This section will be completed by the NHS GG&C Monitoring team and research coordinator.Finance

This is a non-commercial trial funded by the Royal College of Surgeons of Edinburgh (Ophthalmology Small Research Grant of £9,828 awarded March 2019).

19 Insurance

NHS GGC participates in the Clinical Negligence and Other Risks Indemnity Scheme (CNORIS) which has been in operation since 2000. CNORIS covers:

- clinical negligence claims when they arise and are made against members in connection with the acts or omissions of their employees

- non-clinical claims and actions that arise following loss or bodily injury affecting third parties or employees or certain other pecuniary risks

CNORIS will cover GGC employees, both substantive and honorary, who are working in the course of their NHS employment and in respect of conducting research projects which must have received NHS Permission. GGC will not accept liability for any activity that has not been properly registered and Trust approved.

20 Publication policy

All proposed publications will be discussed with Sponsor prior to publishing other than those presented at scientific forums/meetings.

21 Statement of compliance

The trial will be conducted in compliance with the approved protocol, the UK Regulations, GCP and anyapplicable regulatory requirement(s).

22 References

See attachment